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Pharmacokinetics of Daily Daptomycin in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

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Key Words
Antibiotics · Dosing · Gram-positive infection · Renal failure · Renal replacement therapy · Intensive care

Abstract
Background: The optimal daptomycin dosing regimen for critically ill patients undergoing continuous renal replacement therapy (CRRT) has still to be established. ***Methods:*** Daptomycin pharmacokinetics was determined in 9 patients after administration of 6 mg/kg/day over 5 days. ***Results:*** At steady state, which was reached by day 3, the area under the curve over 24 h (AUC24h) was 667.4 ± 356.6 mg · h/l, and the maximum concentration (Cmax) was 66.9 ±25.3 mg/l. Mean CRRT clearance accounted for 48% (range 32–67%) of total clearance (mean 10.2 ml/min, range 6.1–18 ml/min). Significant correlations were observed between Cmax, minimum concentration (Cmin) and AUC24h ($R^2 = 0.91$, $p < 0.001$, and $R^2 = 0.94$, $p < 0.001$) and between albumin plasma concentration and free daptomycin ($R^2 = 0.7$, $p = 0.009$). ***Conclusion:*** No significant accumulation occurred with a daily daptomycin dose of 6 mg/kg in patients undergoing CRRT with an effluent flow rate of >30 ml/kg/h. The quantification of trough concentrations (Cmin) appears to be a good surrogate to estimate AUC24h and to monitor daptomycin treatment in patients undergoing CRRT.

Introduction

Daptomycin is a lipopeptide antibiotic with concentration-dependent bactericidal action against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* spp. [1]. Daptomycin has a molecular weight of 1,620 daltons, is highly protein bound (90–96%) and is mainly eliminated by the kidneys. Renal clearance accounts for about 50% of total daptomycin clearance. About 30% is presumably metabolized in the kidneys and excreted as metabolites and only 5% is excreted in the feces [2]. In *S. aureus* bloodstream infections, including those in patients with right-sided endocarditis caused by methicillin-resistant and methicillin-susceptible strains, the labeled dose is 6 mg/kg every 24 h [3]. As accumulation occurs in patients with renal failure, the dosing interval is prolonged to 48 h in

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patients with severe renal insufficiency (creatinine clearance <30 ml/min) or intermittent hemodialysis [3]. Drug dosing guidelines for continuous renal replacement therapy (CRRT) are often not present in the drug's product labeling, and deduction of dosing recommendations from intermittent hemodialysis can lead to underdosing [4]. Optimal daptomycin dosing in critically ill patients undergoing CRRT has been a matter of debate in recent years. Some authors advocate a dose of 8 mg/kg once every 48 h [5, 6] in order to reach sufficiently high peak concentrations and to avoid high daptomycin trough concentrations and accumulation. Others found very low plasma concentrations at doses of 4 mg/kg every 24 h and recommend a higher dose administered once daily to ensure efficacy [5]. Based on a CRRT model with bovine plasma showing comparable clearance when compared with normal renal clearance [7], we settled for a once daily regimen at our intensive care units at the time. We recently published a retrospective chart analysis of 7 critically ill patients with routinely measured trough and in some cases additional peak concentrations [8]. All of the patients – although undergoing CRRT and receiving daptomycin doses above 6 mg/kg/day once daily in some cases – had daptomycin concentrations below those found in healthy volunteers at the equivalent dose [9, 10]. Therapeutic daptomycin plasma concentrations have not been established so far due to lack of clinical data correlating daptomycin exposure to outcome in patients with Gram-positive infections. Daptomycin shows rapid concentration-dependent killing in vitro with the area under the curve (AUC) over 24 h (AUC24h)/minimal inhibitory concentration (MIC) ratio and peak concentration (Cmax)/MIC ratio being the main determinants of the bactericidal effect [11, 12]. Based on these in vitro results, the European Committee on Antimicrobial Susceptibility Testing suggests a mean AUC24h/MIC target of 438 of total drug for a bacteriostatic effect against susceptible *S. aureus* strains (MIC ≤0.5 mg/l), and for a bactericidal effect, a mean AUC24h/MIC target of 1,061 is recommended [11, 13]. This exposure would theoretically translate into a minimal AUC0–24h of 400 mg · h/l for a bactericidal effect, which is attained with a dose of 6 mg/kg in healthy volunteers [9, 10]. Nevertheless, in severely ill patients with fever in neutropenia and in patients with burn injury considerably lower daptomycin exposure was observed [14, 15]. The aim of this prospective pharmacokinetic (PK) study was to determine the PK of daptomycin administered once daily at a dose of 6 mg/kg in patients undergoing CRRT and to confirm that no significant accumulation occurs with this dosing regimen and that sufficient drug exposure is achieved. Additionally, we investigated the value of Cmax and minimum concentration (Cmin) for monitoring daptomycin exposure.

Materials and Methods

Study Design and Study Population

This prospective PK study was performed in two intensive care units of the University Hospital Zurich, Switzerland. Nine critically ill patients undergoing CRRT because of anuric renal failure who had commenced first-line antibiotic treatment for proven or suspected Gram-positive infection were included. Daptomycin was administered additionally only for study purposes over 5 days. Patients were not included if they had creatinine phosphokinase (CPK) concentrations >2 times the upper normal range, severe liver function impairment (Child class C) or a life expectancy of less than 5 days. If the patient was unable to sign the informed consent, a next of kin and an independent physician had to confirm the presumed will of the patient to participate in the study. The patient was asked for informed consent as soon as he/she regained cognitive functions. Physical examination and laboratory evaluation were performed daily to identify adverse drug effects. In the case of CPK elevation >5 times the upper limit of normal, treatment with daptomycin was stopped. The study (NCT01212432, ClinicalTrials.gov) was approved by the local ethics committee and Swissmedic, the Swiss national regulatory agency. Independent monitoring of protocol adherence was ensured by the Clinical Trial Center at the University Hospital Zurich.

CRRT Procedures

Continuous venovenous hemodiafiltration (CVVHDF) or continuous venovenous hemodialysis (CVVHD) were performed with Multifiltrate (Fresenius Medical Care, Homburg, Germany) using the capillary hemofilter AV 1000s (polysulfone, surface area 1.8 m^2) or with Prismaflex ST150 (Gambro AB, Lund, Sweden) using the capillary hemofilter AN69 ST (acrylonitrile-sodium-methyl sulfonate, surface area 1.5 m^2). The total combined filtration and dialysate rates were maintained between 30 and 40 ml/kg/h if possible. Substitute solutions were usually supplied after the filter, unless repeated clotting made prefilter substitution necessary. The blood flow rate was set between 100 and 200 ml/min.

Drug Administration

Daptomycin (Cubicin®; Novartis, Basel, Switzerland) was diluted in 0.9% sodium chloride and administered intravenously at a dose of 6 mg/kg over 30 min. The drug was given every 24 h on 5 consecutive days.

Sampling and PK Assessments

Extended PK sampling was performed on days 1 and 3. On these days, daptomycin concentrations were determined in arterial blood before daptomycin infusion (Cmin) as well as 0.5 (end of infusion, Cmax), 1, 2, 4, 8, 12 and 24 h after the start of drug administration. Additional samples were taken before and after the filter as well as from the ultrafiltrate twice during these days. Daptomycin concentration was also measured in the urine, which was, if available at all, collected over 24 h. On day 5, only arterial blood samples were taken, 0.5 (Cmax) and 24 h (Cmin) after dap-

Table 1. Patient characteristics

Patient No.	Age, years	Gender	Weight, kg	BMI	Diagnosis	Albumin, g/l	Daily daptomycin dose, mg	CRRT machine/mode/substitution	Mean CRRT effluent flow, ml/kg/h	Mean daily CRRT effluent flow on days 1/3/5, liters/h	CRRT SC[a]	Cl_{CRRT}[a], ml/min
1	80	M	82	32.1	cardiogenic shock, chronic renal failure	26	500	MF/CVVHDF/post	36.9	2.8/2.7/3.6	0.08	3.5
2	64	M	63	21.8	CMV pneumonitis	18	390	MF/CVVHDF/pre	33.8	2.1/2.1/2.2	0.14	3.6
3	70	M	117	36.1	septic shock	20	700	MF/CVVHDF/pre	31.9	4.0/3.6/3.6	0.15	5.7
4[b]	72	M	95	29	septic shock	31	570	MF/CVVHDF/pre	36.8	3.5/–/–	0.11	3.0
5	66	F	70	25.7	sepsis	18	420	PF/CVVHDF/post	32.8	2.1/2.4/2.4	0.16	6.1
6	63	F	42	19.8	renal transplant, intra-abdominal abscess	18	250	MF/CVVHD	69.8	2.2./2.4/2.4	0.16[c]	6.1
7	66	F	120	45.2	septic shock, multiorgan failure	26	700	PF/CVVHDF/post	24.4	4.2/2.4/2.2	0.06	3.8
8	71	M	75	26.2	septic shock, endocarditis	21	450	MF/CVVHDF/post/pre	29.3	2.2/2.2./2.2	0.11	2.5
9	64	M	85	25.3	hemorrhagic shock, liver disease	20	500	MF/CVVHDF/pre	34.5	2.5/3.3/3.0	0.24	6.7
Mean ± SD	68.4 ±5.4		83 ±26	29 ±7.8		22 ±4.6	497.7 ±145.1		36.7 ±13	2.7 ±0.6	0.13 ±0.05	4.5 ±1.5

BMI = Body mass index; CMV = cytomegalovirus; MF = multifiltrate; PF = Prismaflex; post = postdilution; pre = predilution.
[a] Values from day 3. [b] Died on study day 2 for reasons unrelated to the study. [c] Saturation coefficient.

tomycin infusion. The unbound fraction and free daptomycin concentration were determined in all available peripheral arterial blood samples on day 3. Samples were analyzed by liquid chromatography tandem mass spectrometry using a C18 reversed-phase analytical column, 0.1% formic acid and methanol as the mobile phase and electrospray ionization. Heparinized plasma samples were extracted by protein precipitation after the addition of the internal standard (CB 183253). The concentration of daptomycin was calculated by linear regression analysis of the calibration curve ranging from 0.1 to 150 mg/l. The lower limit of quantification of the method was 0.03 mg/l, the precision 3.1% and the accuracy 101%. Unbound daptomycin was estimated by ultrafiltration of plasma using Millipore Centrifugal Filter Units (Merck Millipore, Billerica, Mass., USA). The units were centrifuged for 30 min at 1,000 *g* and 25°C. An aliquot of the ultrafiltrate was prepared as described above and analyzed by liquid chromatography tandem mass spectrometry.

Results are shown as arithmetic means ± standard deviation unless otherwise stated, and p values <0.05 are considered significant. PK parameters were calculated for both total and free daptomycin using standard noncompartmental approaches (WinNonlin 5.3; Pharsight Corp., Mountain View, Calif., USA). Missing trough level data points (Cmin) were estimated by extrapolation using the logarithmic plasma concentrations at the last 2 time points with quantifiable concentrations. AUC was calculated using the linear trapezoidal rule. Cmax and Cmin concentrations were taken directly from the raw data. Total clearance was calculated as dose/AUC at steady state (AUCss). The terminal elimination rate constant (z) was estimated from the slope of the terminal (exponential) phase of the logarithmic plasma concentration-time profile using at least 3 data points. The elimination half-life was determined as 0.693/z. The comparison of PK parameters on days 3 and 5 to baseline values was done using linear mixed effect modeling. Geometric mean ratios and 90% confidence intervals around these ratios were calculated on ln-transformed parameters. No significant difference from baseline was accepted as present if the confidence interval was entirely within the 0.8–1.25 bioequivalence zone. The effect of CRRT on daptomycin clearance (Cl_{CRRT}) was evaluated after measurement of the daptomycin concentration in the venous prefilter blood (Cpre), the venous postfilter blood (Cpost) and the ultrafiltration fluid (Cuf). In cases where CVVHDF was performed in predilution mode, $Cl_{CRRTpre}$ of the prefilter portion was corrected by the dilution factor D and then added to the postfilter and dialysis portion ($Cl_{CRRTpost + dial}$). The sieving coefficient (SC), saturation coefficient and Cl_{CRRT} were determined by the following equations [16]:

SC (saturation coefficient) = 2 × Cuf/(Cpre + Cpost);
Q_{ufd} = sum of ultrafiltrate and dialysate flow rate ($Q_{uf} + Q_d$);
Q_{ufpre} = predilution ultrafiltrate flow rate;
D = blood flow rate/(blood flow rate + replacement fluid rate);
$Cl_{CRRTpre} = D \times SC \times Q_{ufpre}$
$Cl_{CRRTpost + dial} = SC \times Q_{ufpost + d}$
$Cl_{CRRT} = Cl_{CRRTpre} + Cl_{CRRTpost + dial}$

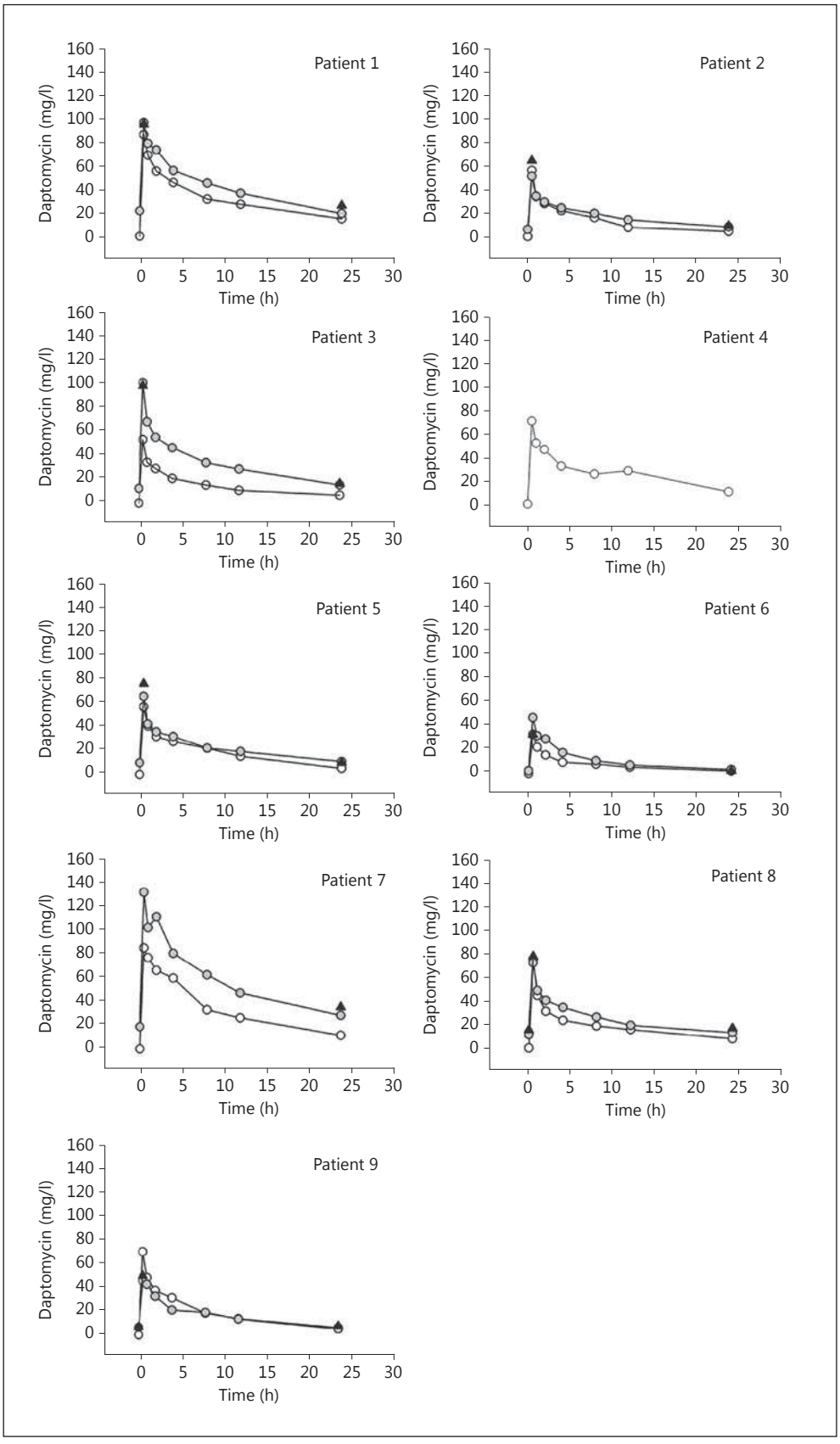

Fig. 1. Individual plasma concentration-time curves of total daptomycin in 9 critically ill patients undergoing CRRT. Day 1: open circles; day 3: shaded circles; day 5: closed triangles.

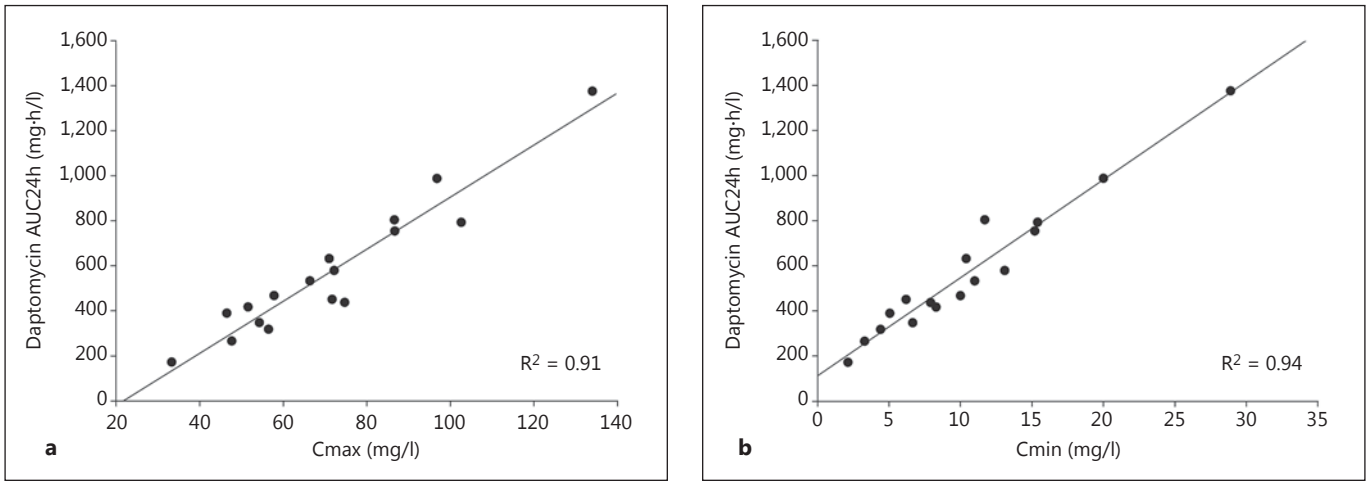

Fig. 2. Individual total daptomycin AUC24h correlated to individual Cmax (**a**) and Cmin (**b**).

Table 2. PK parameters

	Day 1		Day 3				Day 5			
	mean ± SD	GM	mean ± SD	GM	GM ratio day 3/day 1	90% CI of GM ratio	mean ± SD	GM	GM ratio day 5/day 3	90% CI of GM ratio
Cmax, mg/l	65.8±17.1	63.5 (30.5)	77.2±31.3	72.1 (40.8)	1.13	0.83–1.54	66.9±25.3	62.2 (44.1)	0.86	0.62–1.18
Cmin, mg/l	7.7±4.1	6.8 (64.1)	13.1±8.3	10.7 (81.1)	1.58	0.86–2.9	15.6±11.1	11.9 (106.2)	1.1	0.59–2.06
AUC[a], mg·h/l	611±286	548 (55)	667.4±367.6	588.2 (57.6)	1.07	0.70–1.65				
FU, %			22±8							
fAUC24h, mg·h/l			131.3±43							
fCmax, mg/l			15.7±4.9							
$T_{1/2}$, h	10.6±2.4	10.3 (23.1)	12.5±2.3	12.3 (20.8)						
Total clearance, ml/min			10.5±4	13.2 (32.3)						

Values in parentheses represent coefficients of variation. CI = Confidence interval; FU = fraction unbound; GM = geometric mean; fAUC = AUC of free daptomycin; fCmax = free Cmax; $T_{1/2}$ = half-life. [a] Day 1: AUCinfinity; day 3: AUC24h.

Results

Subject Demographics

Baseline characteristics and individual clearance results of the 9 patients are shown in table 1. Eight patients completed the study, and 1 patient died on the second study day for reasons unrelated to the study. Therefore, PK data of the third and fifth days are missing for this patient. The total daily daptomycin dose ranged from 250 to 700 mg (mean 497 ± 145 mg). All patients were anuric (<50 ml of urine per day) during the study period; therefore, no renal clearance was determined. In 8 patients, CVVHDF was used with predilution in 4 patients, and in 1 patient, CVVHD was performed.

PK Results

PK parameters are presented in table 2. Individual plasma concentration-time curves are shown in figure 1. No accumulation between day 1 and day 3 (AUC24h) and no further accumulation from the third to the fifth treatment day (Cmax and Cmin) occurred. The 90% confidence intervals of Cmax and AUC geometric mean ratios were not outside the bioequivalence zone of 0.8–1.25. Cl_{CRRT} varied by up to 2.7-fold between patients, ranging from 2.5 to 6.7 ml/min (mean 4.5 ml/min). Mean CRRT clearance accounted for 48% (range 32–67%) of total daptomycin body clearance (mean 10.2 ml/min, range 6.1–18 ml/min).

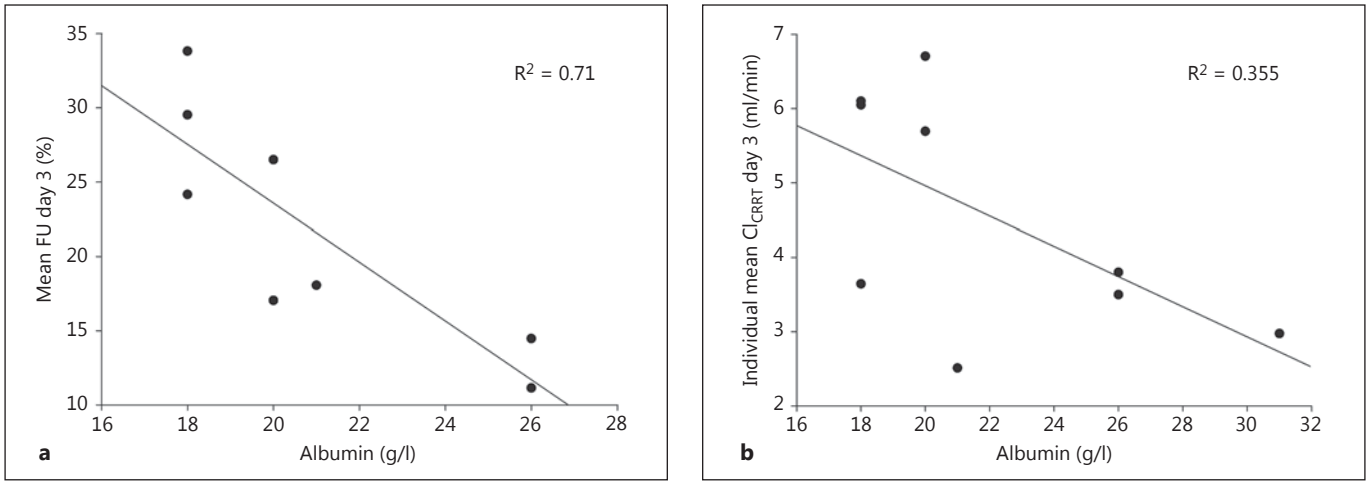

Fig. 3. Individual mean free daptomycin fraction (FU; **a**) and Cl_{CRRT} (**b**) correlated to individual plasma albumin on study day 3.

Table 3. Overview of published daptomycin PK data in CRRT and dosing recommendations

Author (number of patients)	Dosing and timing of PK	CRRT mode (filter type/ surface)	Q_{ufd}, liters/h	SC	FU, %	Cl_{CRRT}, ml/ min	Cl_{tot}, ml/ min	Cmax, mg/l	Cmin, mg/l	AUC48h, mg·h/l	AUC24h, mg·h/l	AUC24–48h, mg·h/l	Dosing recommendation in CRRT
Vilay et al. [18] (8)	8 mg/kg/48 h SD 4 mg/kg/24 h[a]	CVVHD (Optiflux F160NR/1.5 m^2)	2.6±0.3	0.15	0.17	6.3	11.3	81±19[a] 52±12[a]	7±5[a] 12±5[a]	1,060±301[a] 1,052±292[a]			8 mg/kg/48 h
Khadzhynov et al. [5] (8)	8 mg/kg/48 h SD 4 mg/kg/48 h MD	CVVHD (Fresenius PF140 h/1.4 m^2)	2.0	n.d.	n.d.	8.3	11	87.5±15 41±5	5±2.6 2.5±1	899±268 468±84	537±97 302±3	193±69 102±24	>4 mg/kg/24 h
Wenisch et al. [6] (9)	6 mg/kg/24 h PK day 1/day 3	CVVHDF (Prismaflex M100/0.9 m^2)	2.0	0.15	0.16	n.d.	6.9	62±16 78±22	14±6 22±14		555±94		8 mg/kg/48 h
Falcone et al. [23] (6)	6 mg/kg/24 h 8 mg/kg/24 h 6 mg/kg/48 h 8 mg/kg/48 h timing n.d.	CVVHDF (n.r.)[c] CVVHD (n.r.)	n.d.	n.d.	n.d.	n.d.	12/17[b] 9[b] 6[b] 10/9[b]	44/37[b] 61[b] 55[b] 109/61[b]		512[b] 556/607[b]	158/193[b] 566[b]		6 mg/kg/24 h (CVVHDF) 6 mg/kg/48 h (CVVHD)

Cl_{tot} = Total clearance; SD = single dose; MD = multiple dose; n.d. = not determined; n.r. = not reported.
[a] Simulated data at steady state. [b] Individual patient values. [c] Gambro SepteX in 1 patient with 6 mg/kg/24 h multiple dose.

We observed a highly significant linear correlation between daptomycin peak concentrations and AUC24h ($R^2 = 0.91$, $p < 0.001$) and between Cmin and AUC24h ($R^2 = 0.94$, $p < 0.001$; fig. 2a, b). A negative linear correlation of the calculated SC ($R^2 = 0.51$, $p = 0.046$) and the free fraction to albumin ($R^2 = 0.71$, $p = 0.009$) was observed (fig. 3a). Patients with the lowest albumin plasma concentrations (18 g/l) had the highest free daptomycin fraction in plasma (24–34%), while in patients with albumin plasma concentrations of 26 g/l, the unbound fraction ranged from 8.4 to 16.3%. A certain negative correlation was seen with albumin plasma concentrations and Cl_{CRRT} ($R^2 = 0.35$, $p = 0.006$; fig. 3b).

Safety

One potential-drug related adverse event occurred. One patient with pre-existing liver disease had a transient increase of liver enzymes and international normalized ratio on the last study day. He transiently required higher vasopressor doses but stabilized in the consecutive days. No drug-related CPK elevation was recorded in any of the patients.

Discussion

In this study, we investigated the PK of once daily daptomycin at a dose of 6 mg/kg over a period of 5 days in 8 patients treated with CVVHDF and 1 patient undergoing CVVHD. We found that no significant drug accumulation occurred over the study period, and daptomycin exposure at steady state was similar to values found in healthy volunteers with 6 mg/kg/day. Transmembrane clearance of daptomycin in CVVHDF (mean 4.4 ml/min) and CVVHD (6.1 ml/min) was only minimally below renal clearance in subjects with normal renal function (6.5 ml/min) [2], suggesting a sufficient elimination by CVVHDF and also CVVHD. In a CRRT model study with bovine plasma, lower daptomycin clearance values were found in CVVHD compared to continuous hemofiltration at flow rates usually used in clinical practice of 2–3 liters/h (5–8 vs. 7–10 ml/min). The main factors influencing clearance were filter surface and ultrafiltrate and dialysate flow rates [7]. In addition, drug clearance is significantly reduced in continuous hemofiltration by prefilter fluid replacement [17]. This might in part explain similar CRRT clearance values found with CVVHDF in predilution mode compared to CVVHD in our patients. However, definitive conclusions on differences in drug removal efficiency between the two techniques cannot be drawn due to low patient numbers.

Total clearance at steady state in our patients (10.6 ml/min with CVVHDF and 13.4 ml/min with CVVHD) was in the range of clearance values found in healthy subjects (6.1 and 13.3 ml/min) [9, 10]. The proportion of daptomycin excreted by CRRT versus total clearance was also comparable to renal clearance versus total clearance measured in healthy volunteers (48 vs. 50%) [2]. Mean AUCss on the third day (667 mg · h/l) was within the range of values measured in healthy volunteers with the equivalent dose administered at steady state (747 and 632 mg · h/l) [9, 10]. In contrast, mean Cmax was substantially lower on days 3 and 5 (77.2 and 66.9 mg/l) compared to healthy volunteers (98.6 and 93.9 mg/l) [9, 10] and even lower on the first day (65.8 mg/l). A possible explanation might be a higher volume of distribution in critically ill patients with renal failure in consequence of decreased protein binding and fluid overload [4]. The free daptomycin fraction in our patients (22 ± 8%) was higher than values reported by Wenisch et al. [6] and Vilay et al. [18] (16 and 17%, respectively) and more than twice as high as in healthy volunteers (4–10%) [10]. The free fraction correlated significantly with albumin plasma levels (fig. 3a), and a weak correlation of CRRT clearance with albumin (fig. 3b) was found. In consequence, a higher free daptomycin fraction in critically ill patients might add to the relatively high clearance in CRRT.

Daptomycin exposure showed high variability in our patient population. The lowest AUC24h values were 265 mg · h/l (patient 6) and 389 mg · h/l (patient 9), probably due to very low total daily doses and relatively high filtration rates relative to body weight. Both patients did not even meet the bacteriostatic target of AUC24h/MIC >438 recommended by the European Committee on Antimicrobial Susceptibility Testing assuming an MIC of 1 mg/l. Insufficient exposure to daptomycin can lead to treatment failure [19] and bears the risk of selection of resistant strains. Furthermore, daptomycin exhibits lower potency against *Enterococcus* spp., with up to 4-fold higher MICs compared to *S. aureus* [13]. More than doubling of the daptomycin dose was necessary to reach 50% of the maximum effect against *Enterococcus faecium* compared to *S. aureus* in an in vitro pharmacodynamic model [20]. Total drug concentrations measured in our study could therefore theoretically be insufficient to treat *Enterococcus* spp. On the other hand, the relatively high free fraction of daptomycin in critically ill patients might partially overcome the lower total drug exposure. A free AUC/MIC ratio of >40 was associated with bactericidal activity and a minimum risk of emergence of resistance in methicillin-resistant *S. aureus* and vancomycin-resistant *S. aureus* strains [21]. In our patients, a free daptomycin AUC/MIC of 63–400 could be calculated for *S. aureus* strains with an assumptive MIC of 0.5–1 mg/l. Whether this exposure would be sufficient for the treatment of *Enterococcus* spp. is not known.

Steady state was reached on the first treatment day in most of the patients. Only in patients 3 and 7 an AUC increase by 1.4- and 1.7-fold from day 1 to day 3 was observed. The lower exposure on the first PK measurement day coincided with high effluent rates of 4 and 4.2 liters/h, respectively, with a subsequent decrease to 3.6 and 2.4 liters/h on the following PK measurement day. Conversely, in patient 9, the effluent rate was increased on the second day with a decrease in daptomycin exposure indicating an influence of ultrafiltration rates on daptomycin elimination. Minimal accumulation was observed in the remaining patients who had a constant CRRT filtration rate over the study period.

One study reporting PK in extended hemodialysis (ED) [22] and 4 studies investigating the PK of daptomycin in patients undergoing CRRT (table 3) [5, 6, 18, 23] have been published so far. Efficient elimination of

23% daptomycin in ED over 8 h with high-flux filters was found, leading to the conclusion that once daily dosing is appropriate for patients undergoing ED. In the 12 patients undergoing CVVHDF reported by Wenisch et al. [6] and Falcone et al. [23], daptomycin was administered at a dose of 6 mg/kg every 24 h in 11 patients and 8 mg/kg every 24 h in 1 patient. Wenisch et al. [6] determined PK during the first 3 days in 9 patients. An accumulation of daptomycin from the first to the third day by 19% (Cmax) and 60% (Cmin), similar to our findings of 13% (Cmax) and 58% (Cmin), was observed. Mean AUC24h on the third day was still below our AUCss value (555 vs. 667 mg · h/l). In contrast to our study, they did not determine daptomycin plasma concentrations on the subsequent days. Based on an additional dosing simulation with a dose of 8 mg/kg every 48 h, the authors suggest that a dose of 8 mg/kg every 48 h would be appropriate to avoid accumulation and high trough levels. Even lower AUC24h values were found by Falcone et al. [23] in the 2 patients receiving 6 mg/kg every 24h (158 and 193 mg · h/l). The very low exposure was attributed to the use of a high cutoff filter in 1 patient, but in none of the patients timing of sampling, ultrafiltration rates or clearance values were reported. In the patient who had received 8 mg/kg daptomycin every 24 h, AUC24h was 566 mg · h/l. Nevertheless, the authors suggest that 6 mg/kg every 24 h is the optimal dose in CVVHDF.

In the studies using CVVHD [5, 18, 22], daptomycin was administered every 48 h to all of the 18 patients reported. While CVVHD settings in the studies of Vilay et al. [18] and Khadzhynov et al. [5] were comparable to our settings, again no information on this issue is provided by Falcone et al. [23]. Vilay et al. [18] determined single-dose PK over 48 h and simulated steady-state PK for dosing of 8 mg/kg every 48 h and 4 mg/kg every 24 h. Simulated AUC48h values were similar for the two dosing regimens. The authors conclude that daptomycin dosing of 8 mg/kg every 48 h would be more appropriate in patients undergoing CVVHD in order to reach sufficient peak concentrations and avoid trough levels above 20 mg/l, although only 1 patient had a simulated Cmin at steady state of >20 mg/l. Falcone et al. [23] recommend dosing of 6 mg/kg every 48 h based on the fact that AUC48h values in the CVVHD patients were similar to AUC24h values in their CVVHDF patients who received daptomycin at 6 mg/kg every 24 h. However, AUC48h should be twice as high as AUC24h for a similar AUC over 48 h. Hence, a very low daptomycin exposure, especially on the second day, must be assumed. The low AUC48h indicates that even in CVVHD patients, a once daily dosing of 6 mg/kg might have been appropriate, provided that similar CVVHD settings were used. In fact, Khadzhynov et al. [5] recommend once daily dosing of at least 4 mg/kg based on very low daptomycin exposure over 24–48 h in the 8 CVVHD patients studied with a dosing interval of 48 h.

Despite the fact that higher Cmax is reached with doses of 8 mg/kg, we think that this advantage has to be balanced against the risk of loss of bactericidal effect when the dosing interval is extended from 24 to 48 h [24]. Our data strongly support the recommendation made by Khadzhynov et al. [5] and confirm that once daily dosing of 6 mg/kg is necessary to achieve adequate daily daptomycin concentrations without a risk of overdose in patients undergoing CVVHDF and probably also in CVVHD with comparable hemodialysis rates. Particularly in critically ill patients with often severe Gram-positive infections, higher daptomycin exposure might be more favorable as the drug exhibits a concentration-dependent antimicrobial effect.

Close correlations of Cmax and Cmin with AUC24h were observed (fig. 2). Measurement of AUC by extensive PK sampling is time-consuming, expensive and error prone in clinical routine; therefore, monitoring of Cmax or Cmin might be a valuable alternative to estimate AUC and to ensure adequate daptomycin exposure in critically ill patients undergoing CRRT. Since, in contrast to other studies in critically ill patients, we intensively collected samples for daptomycin quantification on the first 5 treatment days, our results robustly show the usefulness of Cmax and Cmin quantification for AUC24h estimation.

A shortcoming of our study is the small number of participants, which translated into large 90% confidence intervals and reflects the large variability in daptomycin PK. However, recruitment of critically ill patients in an intensive care unit is difficult, as confirmed by the low number of participants in other studies on comparable populations.

Conclusion

In conclusion, daptomycin PK in patients undergoing CVVHDF or CVVHD at rates of 30–40 ml/kg/h were comparable to those in healthy volunteers. We showed that no further accumulation occurred after the third treatment day with once daily dosing. Hence, we suggest at least 6 mg/kg daptomycin once daily should be given

to critically ill patients undergoing CVVHDF and most probably also in CVVHD. Monitoring of daptomycin concentrations seems advisable in view of the variability in drug clearance and daptomycin plasma concentrations in patients undergoing CRRT. The quantification of trough concentrations (Cmin) appears to be a good surrogate to estimate AUC24h values. However, therapeutic ranges remain to be established and validated in future studies.

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Disclosure Statement

Dr. Corti was a member of the Cubicin advisory board for Novartis Switzerland. Drs. Rudiger, Chiesa, Rentsch, Jetter, Béchir, Maggiorini and Marti have no potential conflicts of interest to disclose.

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